REMARKS

I. Claim Amendment

Claim 1 is amended to recite that the rAAV-producing cell insert is modified to overexpress AAV Rep 52 and Rep 40 proteins. This amendment is supported throughout the specification, *e.g.* at page 4, line 22 through page 5, line 6. This amendment does not add new matter to the application.

II. The Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

Claims 6 and 7 were rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. The Examiner stated that these claims encompass novel biological material and these materials must be attainable by methods taught in the specification or otherwise readily available to public. The specification teaches how to generate the claimed cells at page 11, line 5 through page 6, line 24. However, in order to expedite prosecution, claims 6 and 7 are canceled without prejudice. Therefore, the rejection under 35 U.S.C. § 112, first paragraph is moot and should be withdrawn.

III. The Rejection Under 35 U.S.C. § 102 Should be Withdrawn

The rejection of claims 1-3, 10-13, 18, 21, 23, 24, 30, 32 and 33 under 35 U.S.C. § 102(b), as allegedly being anticipated by Natsoulis *et al.* (U.S. 6,027,931), was maintained. In particular, the Examiner asserted that Natsoulis *et al.* teaches constructs pRCM.kozak and pRCM.polyA, which allegedly express Rep78/68 at a level produced when expression of the proteins is under the control of the p5 promoter, and express Rep52/40 at a level greater than the control. The Examiner's statements regarding the expression levels of Rep78/68 and Rep52/40 are based on his evaluation of the Western blot data in Fig. 2 of Natsoulis *et al.* Applicants continue to dispute that Natsoulis *et al.* anticipates the pending claims.

None of the vectors taught in Natsoulis *et al.* express Rep78/68 at the level when expressed under the control of the AAV p5 promoter in its native conformation and overexpress Rep52/40 as recited in the pending claims. According to the text of the Natsoulis *et al.*, the genetic alterations within vectors pRCM.kozak and pRCM.polyA had "little effect

on Rep protein expression." Moreover, Natsoulis *et al.* does not state that the low molecular weight protein bands in Figure 2, lanes 4 and 5 demonstrate an overexpression of Rep52/40 by these vectors. This is the Examiner's own interpretation of the reproduction of the gel. In the experiments described in Natsoulis *et al.*, nothing is done to increase the expression of Rep52/40 proteins. Even if the low molecular weight protein bands, in lanes 4 and 5 of Figure 2, are more intense, this was not due to purposeful overexpression as required by the present claims and may be normal variation in protein expression rather than an overexpression. Therefore, the methods/vectors taught in Natsoulis *et al.* do not literally or inherently anticipate or render obvious pending claim 1.

Furthermore, claim 1 requires that the level of expression of AAV Rep78 and Rep 68 not be genetically down-regulated in the recited cell. The Natsoulis *et al.* vectors pRCM.kozak and pRCM.polyA have been modified in an attempt to genetically down-regulate Rep 78 and Rep 68 expression. According to Natsoulis *et al.*, these vectors had a "[m]odification of the Kozak sequence as to reduce translation initiation efficiency (pRCM.kozak; lane 4) and introduction of a sub-optimal polyadenylation site between the transcriptional start site and the first codon in the coding sequence of the long forms of Rep p[proteins (pRCM.polyA; lane 5)." (see column 15, lines 52-56).

The Examiner also indicated the rejection of claims 3 and 10 was maintained based on the argument that Natsoulis *et al.* taught the addition of Rep/Cap expression constructs sequentially to cells. Claim 3 requires that an expression cassette encoding Rep 52 and Rep 40 proteins be subsequently introduced into a cell already comprising a rAAV genome, AAV rep-cap proteins and AAV helper functions. Natsoulis *et al.* does not teach this. Similarly, claim 10 requires that supplemental Rep 52 and Rep 40 proteins be introduced into a cell already comprising a rAAV genome and AAV rep-cap proteins. Again, Natsoulis *et al.* does not teach this. The methods in Natsoulis *et al.* involves **one** transfection of 10 micrograms of **one** of six different rep-cap protein-encoding constructs. There is no second introduction of rep-cap sequences or proteins described in Example 1. Each 293 cell line is transfected only once with one rep-cap construct. See Natsoulis *et al.* Example 1 as well as the data presented in Table 1.

Natsoulis *et al.* column 12, lines 39-42 states that an AAV vector and AAV helper function vector can be sequentially transfected into a host cell. Regarding how the two vectors are supposed to work with respect to each other, column 7, lines 1-12 of Natsoulis *et al.* states that AAV helper functions include the rep and cap regions and are used to complement AAV functions that are missing from AAV vectors. Assuming that is the case, then the sequential transfection of column 12 is not a sequential transfection of rep-cap sequences. Therefore, neither independent claims 3 and 10 nor claims dependent thereon are expressly or inherently anticipated by Natsoulis *et al.* and the rejection of those claims under U.S.C. §102(b) should be withdrawn.

The Examiner maintained the rejection of claim 18 and the claims dependent thereon. As stated previously, claim 18 requires infection by an infectious simian adenovirus (Ad), while Natsoulis *et al.* expressly excludes "adenovirus (Ad)" from the definition of "accessory function vector" at column 7, lines 64-66.

In view of the foregoing remarks, claims 1-3, 10-13, 18, 21, 23, 24, 30, 32 and 33 are not expressly or inherently anticipated by Natsoulis *et al.* Therefore, the rejection under 35 U.S.C. § 102 should be withdrawn.

IV. The Rejection under 35 U.S.C. § 103(a) Should Be Withdrawn

The Examiner maintained the rejection of claims 22, 26, 28, 29, 31, 35, 37 and 38 under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* (U.S. Patent No. 6,027,931) in view of Hardy (U.S. Patent No. 6,429,001). The Examiner stated that Hardy teaches that AAV host cells include the claimed cell types: HeLa, WI-38, MRC-5 and Vero. Similarly, claims 25 and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Murphy (U.S. Patent No. 6,635,476). The Examiner stated that Murphy teaches that the PERC.6 cells line is useful for producing adenovirus and rAAV. Claims 27-29 and 36-38 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Potash *et al.* (U.S. Patent No. 5,911,998). The Examiner stated that Potash *et al.* teaches that the MRC-5, WI-38 and FRhL-2 cell lines may be used for vaccine production.

In addition, the Examiner rejected claims 4, 5 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Natsoulis *et al.* in view of Collaco *et al.* (*Gene* 238:397-405, 1999). The Examiner stated that Collaco teaches the production of rAAV using pSH3 and pSH5 vectors that comprise E4, E2a and VA genes. The Examiner also rejected claims 9, 14 and 19 under §103(a) as being unpatentable over Natsoulis *et al.* in view of Collaco (*Gene* 238:397-405, 1999) and in further view of Gao *et al.* (U.S. Patent No. 7,235,393). The Examiner asserted that Gao *et al.*, teaches that any available adenovirus would be useful for production of rAAV, including those from simian species such as SV-35 and SV-25.

As the primary document, Natsoulis *et al.*, cited in the rejection does not teach or suggest methods according to the claims (see Section II above), combinations of it with other documents that similarly do not teach or suggest methods as claimed do not render the claims obvious. Therefore, the rejections under 35 U.S.C. § 103(a) should be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants believe pending claims 1-5, 8-14, 18, 19 and 21-38 are in condition for allowance and early notice thereof is requested. If further discussion would expedite allowance of the claims, the undersigned can be contacted at the telephone number below.

Respectfully submitted,

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